Amendments to the Specification:

On page 1 of the specification, delete the title starting with "RIBOSOME STRUCTURE" and ending with "INHIBITORS" and replace with the following new title:

-- MODULATORS OF RIBOSOMAL FUNCTION AND IDENTIFICATION THEREOF --

On page 1, immediately after the heading **REFERENCE TO RELATED APPLICATIONS**, replace the paragraph beginning with "This application" and ending with "reference herein." with the following new paragraph:

-- This application is a continuation-in-part of co-pending application of U.S. Application No. 09/922,251, filed August 3, 2001, and claims the benefit of (i) U.S. Provisional Application No. ~~[Attorney Docket No. RIB-003PR]~~ 60/348,731, filed January 14, 2002, and (ii) U.S. Provisional Application No. ~~[Attorney Docket No. RIB-004PR]~~ 60/352,024, filed January 25, 2002, the disclosures of each of which are incorporated by reference herein. --

Please amend the paragraph bridging pages 13 and 14 to read as follows:

-- In a preferred embodiment, the atomic co-ordinates further define at least a portion of a protein synthesis inhibitor, for example, an antibiotic, more specifically an antibiotic selected from the group consisting of anisomycin, blasticidin, carbomycin A, sparsomycin, spiramycin, tylosin, virginiamycin M, azithromycin, linezolid, chloramphenicol and erythromycin, complexed with a ribofunctional locus. More specifically, the invention provides atomic co-ordinates of the large ribosomal subunit together the atomic co-ordinates of antibiotics interacting with the large ribosomal subunit. These atomic co-ordinates are recorded on compact disk, Disk No. 1, and correspond to: large ribosomal subunit complexed with anisomycin (file name: anisomysin.pdb or ANISOMYC.PDB); large ribosomal subunit complexed with blasticidin (file name: blasticidin.pdb [[~~r~~]] or BLASTICI.PDB); large ribosomal subunit complexed with carbomycin (file name: carbomycin.pdb or CARBOMYC.PDB); large ribosomal subunit complexed with tylosin (file name: tylosin.pdb or TYLOSIN.PDB); large ribosomal

subunit complexed with sparsomycin (file name: sparsomycin.pdb or SPARSOMY.PDB); large ribosomal subunit complexed with virginiamycin M (file name: virginiamycin.pdb or VIRGINIA.PDB); large ribosomal subunit complexed with spiramycin (file name: spiramycin.pdb or SPIRAMYC.PDB); large ribosomal subunit complexed with azithromycin (file name: AZITHROM.PDB or azithromycin.pdb); or large ribosomal subunit complexed with linezolid (file name: LINEZOLI.PDB or linezolid.pdb); or large ribosomal subunit complexed with erythromycin (file name: erythromycin.pdb). --

Please amend the paragraph bridging pages 32 and 33 to read as follows:

-- As used herein, the term "atomic co-ordinates" or "structure co-ordinates" refers to mathematical co-ordinates (represented as "X," "Y" and "Z" values) that describe the positions of atoms in a crystal of a ribosome or ribosomal subunit. The diffraction data obtained from the crystals are used to calculate an electron density map of the repeating unit of the crystal. The electron density maps are used to establish the positions of the individual atoms within a single ribosomal subunit. Those of skill in the art understand that a set of structure co-ordinates determined by X-ray crystallography is not without standard error. For the purpose of this invention, the structures of two ribosomes, ribosomal subunits or portions thereof are considered to be the same if they satisfy one of the following two tests. In a first test, the structures are considered to be the same if a set of structure co-ordinates for a ribosome or ribosomal subunit from any source has a root mean square deviation of non-hydrogen atoms of less than about 2.0 Å, or more preferably less than about 0.75 Å, when superimposed on the non-hydrogen atom positions of the atomic co-ordinates deposited at the Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank (PDB) (Berman *et al.* (2000) *Nucleic Acids Research* 28, 235-242; see also, the web page at URL ~~http://www.~~rcsb.org/pdb/) with the accession numbers PDB ID: 1FFK; PDB ID: 1FFZ; PDB ID: 1FG0; PDB ID: 1JJ2;PDB ID: 1K73; PDB ID: 1KC8; PDB ID: 1K8A; PDB ID: 1KD1; or PDB ID: 1K9M, or contained on Disk 1 of 1, the disclosure of each of the foregoing of which is incorporated herein by reference in its entirety. In a second test, the structures are considered to be the same if the r.m.s. deviation between a set of atoms in a test structure and a corresponding set of atoms in a reference structure is less than 2.0 Å. For the purposes of this test, the set of atoms in the reference structure comprises at least

five of the series of 23S rRNA residues listed below as 631-633, 835-841, 844-846, 882-885, 1836-1839, 2095-2105, 2474-2478, 2485-2490, 2528-2530, 2532-2543, 2607-2612, 2614-2623, 2642-2648 of the structure deposited in the PDB under accession number PDB ID: 1JJ2 or contained as file name ~~1jj2.rtf~~ 1JJ2.RTF on Disk 1 of 1. The residues in the test structure corresponding to the ones listed above are identified by sequence alignment using the program Lasergene v. 5.0 (DNA Star, Inc., Madison, WI) with the default settings. Specifically, the computer program is used to align those residues listed above in the *Haloarcula marismortui* 23S rRNA sequence with those in the test organism's rRNA. Once aligned, the corresponding residues in the test organism's rRNA are identified. The atomic co-ordinates of backbone atoms (P, C5', 05', C4', C3', 03') of atoms in the test structure are superimposed upon the corresponding backbone atoms (P, C5', 05', C4', C3', 03') of the reference structure using the program MIDAS Plus (Ferrin *et al.* (1988) *J. Mol. Graphics* 6: 13-27 and 36-37). The test and reference structures are considered the same if the r.m.s. deviation between the two sets of atoms after superpositioning is less than 2.0 Å, as determined by MIDAS Plus. --

Please amend the first full paragraph appearing on page 34 to read as follows:

-- Reference is made to the sets of atomic co-ordinates and related tables included with this specification and submitted on compact disk (two total compact disks including one original compact disk, and a duplicative copy of original compact disks). Disk No. 1 contains thirty-nine files. Disk No 1 contains the files identified as PDB1FFK.DOC and PDB1FFK.ENT which represent files of co-ordinates defining the large ribosomal subunit; PDB1FFZ.DOC and PDB1FFZ.ENT which represent files of the co-ordinates defining the large ribosomal subunit - CCdA-p-Puro complex; and PDB1FGO.DOC and PDB1FGO.ENT which represent files of the co-ordinates defining the large ribosomal subunit - aa-tRNA analogue complex; 1JJ2.RTF and 1JJ2.TXT which represent files of the co-ordinates defining the completely refined large ribosomal subunit; anisomycin.pdb, blasticidin.pdb, carbomycin.pdb, sparsomycin.pdb, spiramycin.pdb, tylosin.pdb and virginiamycin.pdb which represent files of the co-ordinates defining the large ribosomal subunit bound to anisomycin, blasticidin, carbomycin, sparsomycin, spiramycin, tylosin, and virginiamycin, respectively; three folders: FOLDERA contains the file identified as 1JJ2.PDB (which represents a file of a more highly refined co-ordinates defining the

large ribosomal subunit), FOLDERB contains the files identified as ANISOMYC.PDB, BLASTICI.PDB, CARBOMYC.PDB, SPARSOMY.PDB, SPIRAMYC.PDB, TYLOSIN.PDB, and VIRGINIA.PDB (which represent files of the refined co-ordinates defining the large ribosomal subunit bound to anisomycin, blasticidin, carbomycin, sparsomycin, spiramycin, tylosin, and virginiamycin, respectively), FOLDERC contains the files identified as AZITHROM.PDB, and LINEZOLI.PDB (which represent files of the co-ordinates defining the large ribosomal subunit bound to azithromycin and linezolid, respectively); the file identified as erythromycin.pdb (which represents a file of the co-ordinates defining the large ribosomal subunit bound to erythromycin), and azithromycin.pdb and ~~linezolid.pdp~~ linezolid.pdb (which represent files of the refined co-ordinates defining the large ribosomal subunit bound to azithromycin and linezolid, respectively). --

Please amend the first full paragraph appearing on page 37 to read as follows:

-- As used herein, the term "homologue" is understood to mean any one or combination of (i) any protein isolated or isolatable from a ribosome or a ribosomal subunit (*i.e.,* a ribosomal protein), (ii) any nucleic acid sequence isolated or isolatable from a ribosome or ribosomal subunit (*i.e.,* a ribosomal RNA), (iii) any protein having at least 25 % sequence identity to a ribosomal protein isolated from *E. coli* or *Rattus norvegicus* as determined using the computer program "BLAST" version number 2.1.1 implementing all default parameters, or (iv) any nucleic acid having at least 30% sequence identity to a ribosomal RNA isolated from *E. coli* or *Rattus norvegicus* as determined using the computer program "BLAST" version number 2.1.1 implementing all default parameters. "BLAST" version number 2.1.1 is available and accessible via the world wide web at ~~http://www/~~ the URL ncbi.nlm.nih.gov/BLAST/ or can be run locally as a fully executable program on a standalone computer. --

Please amend the paragraph bridging pages 40 and 41 to read as follows:

-- The present invention is also based, in part, on the atomic structure of the crystal of the 50S ribosomal subunit from *H. marismortui* that has been derived from a 2.4 Å resolution electron density map that was experimentally phased using heavy atom derivatives. The atomic co-ordinates defining the large ribosomal unit were deposited on July 10, 2000, at Research

Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank (PDB) (Berman *et al.* (2000) *Nucleic Acid Research* 28, 235-242; ~~http:// www.~~ see also, the web page at the URL rcsb.org/pdb/) with accession number PDB ID: 1FFK. --

Please amend the second full paragraph appearing on page 57 to read as follows:

-- Analysis of the atomic co-ordinates discussed in section IIA above together with additional atomic co-ordinates of a ribosomal subunit complexed with various analogues, similarly refined, permit an analysis of ribosome function. Accordingly, the present invention is also based on the crystals of *Haloarcula marismortui* 50S ribosomal subunit complexed either with the Yarus transition state analogue, CCdA-p-Puro, or with a mini-helix analogue of an aminoacyl-tRNA. The present invention provides the structures of both complexes. The atomic co-ordinates of the structure of both complexes were deposited on July 26, 2000, at Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank (PDB) (Berman *et al.* (2000) *Nucleic Acid Research* 28: 235-242; ~~http:// www.~~ see also, the web page at the URL rcsb.org/pdb/) with accession numbers PDB ID: 1FFZ (50S ribosome/ CCdA-p-Puro complex) and PDB ID: 1FG0 (50S ribosome/aa-tRNA analogue). --

Please amend the paragraph bridging pages 81 and 82 to read as follows:

-- By way of example, since the nucleotide sequences of all known 50S subunit rRNAs can be aligned relative to each other and to *H. marismortui* 23S and 5S rRNAs, it is possible to construct models of the structures of other 50S ribosomal rRNAs, particularly in the regions of the tunnel and active sites, using the *H. marismortui* structure. Likewise, homologous proteins can also be modeled using similar methodologies. Methods useful for comparative RNA sequence analysis are known in the art and include visual methods and number pattern methods, as well as methods employing chi-square statistics, phylogenetic algorithms, or empirical algorithms. Descriptions of some of the foregoing methods are available, for example, ~~at http://www.~~ on the world wide web at the URL rna.icmb.utexas.edu/; Gutell (1996), "Comparative Sequence Analysis and the Structure of 16S and 23S rRNA," Ribosomal RNA. Structure, Evolution, Processing, and Function in Protein Biosynthesis, (Dahlberg A. and Zimmerman B., eds.) CRC Press. Boca Raton, pp. 111-128; Guttell *et al.* (1993) *Nucl. Acid Res.*

21:3055 - 3074; Schnare *et al.* (1996) *J. Mol. Biol.* 256: 701-719. Particularly useful visual inspection methods include comparison of a particular position in a *H. marismortui* secondary structure diagram with the residues located at the analogous position on an *E. coli* secondary structure diagram. A software program that is particularly useful in homology modeling includes XALIGN (Wishart, D. *et al.*, (1994) *Cabios* 10: 687-88). See also, U.S. Patent No. 5,884,230. --

Please amend the second full paragraph appearing on page 184 to read as follows:

-- The disclosure of each of the patent documents, scientific articles, atomic-co-ordinates (including, without limitation, those sets deposited at the Research Collaboratory for Structural Bioinformatics Protein Data Bank (PDB) with the accession numbers PDB ID: 1FFK; PDB ID: ~~1FF2~~ 1FFZ; PDB ID: 1FG0; PDB ID: 1JJ2; PDB ID: 1K73; PDB ID: 1KC8; PDB ID: 1K8A; PDB ID: 1KD1; and PDB ID: 1K9M, and/or contained on Disk No. 1) referred to herein is incorporated by reference herein. --